FDG Positron Emission Tomography-Breast Cancer
#CAG-00094A
Decision Memorandum

To: File: FDG Positron Emission Tomography (PET)-Breast Cancer CAG-00094A

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Re: Coverage Decision Memorandum on FDG PET for Breast Cancer

Date: February 27, 2002

This memorandum serves three purposes: (1) provides background for this coverage decision memorandum; (2) analyzes relevant scientific and clinical literature related to the use of PET scans as a diagnostic tool for breast cancer; and, (3) outlines the agency's intention to change its national coverage determination (CIM 50-36) under the statutory authority at §1862(a)(1)(A) of the Social Security Act (the Act).

Background

Positron-emitting radioisotopes are used to evaluate glucose metabolism and blood perfusion in normal cell function, as well as altered metabolism in diseases like cancer, ischemic heart disease, and some neurological disorders. 2-[F-18] Fluoro-D-Glucose (FDG) is an injected radioactive tracer substance (radionuclide) that gives off sub-atomic particles, known as positrons, as it decays. PET is a minimally-invasive diagnostic procedure using a positron camera (tomograph) to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on glucose metabolism in a given cell. This information is then used to diagnosis various diseases.

Existing technology, such at computerized tomography (CT) and magnetic resonance imaging (MRI), supplies information about the anatomic structure of suspected malignancies, primarily their size and location. FDG's utility in cancer imaging is its ability to differentiate lesions based on cellular biochemical or physiologic function. Detecting increased glucose metabolism within cancer cells is unique to PET technology. Additionally, PET applies mathematical models to the obtained metabolic information. This provides objective, rather than visual, interpretation of clinical findings.

Breast cancer is the most common non-skin malignancy in United States women, accounting for nearly 30 percent of newly diagnosed cancers, with an incidence of 182,800 cases and 53,000 mortalities in the year 2000. A woman has a 1 in 8 chance of being diagnosed with breast cancer during her lifetime. Although the exact etiology of breast cancer remains unknown in a majority of cases, many endogenous and exogenous factors have been implicated in the development of the disease. These include genetic mutations and other hereditary influences, endocrine factors, previous radiation exposure, diet, cigarette smoking, alcohol consumption, and other environmental and lifestyle determinants.

Food and Drug Administration (FDA) Status

The Food and Drug Administration approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language.

> "This new drug application provides for the use of Fludeoxyglucose F-18 Injection for the following indications:
>
> 1. Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
> …
> We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter…."

Timeline

On July 10, 2000, CMS received a request for broad coverage of FDG PET scans from Drs. Michael Phelps and Sam Gambhir. The requestors stated that measurement of FDG by a PET scan can aid in the diagnosis and treatment of 22 medical conditions that included various oncological indications (such as breast cancer), myocardial viability, and neurological indications. CMS determined that the appropriate benefit category for all of the requested indications fell under §1861(s)(3) of the Social Security Act - diagnostic services.

On December 15, 2000, CMS published a decision memorandum on this request for broad coverage (CAG-00065) of all oncological indications, heart disease, and neurological disorders. The December 15th decision memorandum stated that CMS had insufficient evidence to support coverage for the indication of breast cancer at that time but would refer the issue to the Medical Coverage Advisory Committee (MCAC). The full December 15th decision memorandum is available at www.hcfa.gov/coverage/8b3-hh2.htm.

On March 7, 2001, CMS referred the issue to the Agency for Healthcare Research and Quality (AHRQ) for a technology assessment. The technology assessment was performed by the Blue Cross and Blue Shield Association Technology Evaluation Center, one of the evidence-based practice centers (EPC's) contracted by AHRQ. The full technology assessment is available at www.hcfa.gov/coverage/download/8b1-g1.pdf.

On June 19, 2001, the Medicare Coverage Advisory Committee (MCAC) Diagnostic Imaging Panel deliberated on the issue of FDG PET for breast cancer and made its recommendation regarding the evidence on efficacy to the MCAC Executive Committee. The MCAC Executive Committee reviewed and approved the Diagnostic Imaging Panel's recommendation to CMS on October 17, 2001, with the exception of amending question number 4 to state, "is it likely that PET improves health outcomes when used as an adjunct to standard staging tests in detecting locoregional recurrence or distant metastases recurrence for some patients when results from other tests are inconclusive."

Technology Assessment

The technology assessment focused on whether the use of PET could improve health outcomes for the following:

A. Initial diagnosis of breast cancer;
B. Initial staging of axillary lymph nodes;
C. Detection of locoregional recurrence or distant metastasis/recurrence; and
D. Evaluating response to treatment.

Articles accepted for review by the Blue Cross and Blue Shield Association Technology Evaluation Center had to meet selection criteria specific to indication A through D, above. These criteria can be found at www.hcfa.gov/coverage/download/8b1-g1.pdf**.**

A. Initial Diagnosis of Breast Cancer

In addressing the use of PET for initial breast cancer diagnosis, the technology assessment addressed two different patient indications:

- Patients who have an abnormal mammogram or palpable breast mass and are recommended to undergo biopsy diagnosis, and

- Patients who have a low suspicion finding on mammography and are referred for short-interval (i.e., 3-6 month) imaging follow-up.

For the first indication, thirteen studies (total n=606) met the selection criteria and were included for review and analysis[1]. A meta-analysis of these studies yielded a sensitivity of 89% and a specificity of 80% when PET is used for this indication. The gold standard for tissue diagnosis is via cytologic or histologic sampling.

With respect to study design, the technology assessment raised several concerns. Only 3 of the 13 studies confirmed that consecutive patients were used to avoid selection bias. In addition, 7 of the 13 studies clearly indicated that interpreters of PET results were blinded to the results of clinical findings or other imaging tests. However, none of the studies provided sufficient information to determine whether clinical findings or other imaging tests were interpreted blind to PET results. While all studies utilized histological findings as the reference standard, 3 studies were unable to gather histology on all patients (using findings from either fine needle aspiration or core biopsy for some patients). Finally, 3 of the studies were retrospective reviews, and 5 studies utilized a sample size of 20 or fewer patients.

In addition to concerns related to study quality, the technology assessment also raised questions about the applicability of the studies to a larger population. Mean tumor size across the studies ranged from 2 to 4 cm. Further, the prior probability of malignancy in the available studies ranged from 53% to 95%. The relatively large tumor size and high probability of malignancy suggest that the conclusions of these studies may not be applicable to populations with smaller tumor sizes and a lower probability of malignancy.

The technology assessment concluded that, among study populations with large tumor sizes and higher prevalence of malignancy, "…the risk of a false-negative diagnosis is likely too high relative to the benefit of avoiding biopsy of a benign lesion". Evidence is not available to permit conclusions about the use of PET for patients with small, nonpalpable lesions.

For the second indication under initial diagnosis of breast cancer (e.g., patients with low suspicion findings on mammography who are referred for short-interval follow-up), no studies meeting the study selection criteria could be identified. Thus, no definitive conclusions could be drawn for this clinical indication.

B. Initial Staging of Axillary Lymph Nodes

For this clinical indication, PET is proposed for selecting patients that need to undergo axillary lymph node dissection from among those patients who have no clinically palpable axillary adenopathy. The study population for this indication includes patients with a confirmed primary breast malignancy, no palpable axillary lymph node metastases, and no evidence of distant metastases.

[1] Five articles met selection criteria but were excluded due to the possibility that the patient population may overlap with a later report from the same institution.

The technology assessment identified four studies meeting the study selection criteria that reported on the use of PET for patients with nonpalpable axillary lymph nodes[2]. Among these patient nodal regions (total n=203), sensitivities ranged from 40% to 93% and specificities ranged from 87% to 100%. The meta-analysis yielded a sensitivity of 81% and a specificity of 95% when PET is used for this indication.

In terms of study design, the technology assessment indicated that only one of the four studies provided information to confirm that selection bias was avoided through the use of consecutive patients. Three of the four studies provided clear information that PET studies were interpreted blind to other imaging and clinical findings, and none of the studies provided information to determine whether clinical findings or other imaging tests were interpreted blind to PET results. All of the studies utilized a prospective design and histology (axillary lymph node dissection) results as the reference standard, though one study utilized cytologic results (fine needle aspiration) rather than histologic results for 10% of patients in the study (5 of 50).

The technology assessment concluded that the available body of evidence is "…too sparse to draw conclusions regarding the diagnostic performance of PET for staging of axillary lymph node metastases". The conclusion was based on the following factors: a low number of total patients in the available studies (total n=203); the very wide confidence interval for sensitivity estimates from meta-analysis; and a false-negative rate that is "…too high to support a favorable risk/benefit ratio from using PET to avoid axillary lymph node dissection".

C. Detection of Locoregional Recurrence or Distant Metastasis/Recurrence

For patients with an initial diagnosis of breast cancer, accurate identification and assessment of metastatic disease is crucial for guiding individual treatment decisions. Evaluation for the spread of disease may occur at the initial diagnosis of breast cancer or following previous treatment for the disease. For the purpose of staging the spread of disease, PET has been proposed as either an adjunct to, or replacement for conventional imaging modalities.

With respect to locoregional recurrence, the technology assessment identified two studies (total n=85) meeting study selection criteria. In one study (n=10), the reported sensitivity and specificity values for PET were both 100% (Hathaway et al.1999). A second prospective study (n=75) reported diagnostic performance of PET for local recurrence and in lymph nodes (Bender et al.1997). For local recurrence, the sensitivity value for PET was 80% (compared to 93% for computerized tomography (CT)/magnetic resonance imaging (MRI)) and the specificity value for PET was 96% (compared to 98% for CT/MRI). In lymph nodes, the reported sensitivity of PET was 97% (versus 74% for CT/MRI) and the reported specificity was 91% (versus 95% for CT/MRI). The

[2] Five additional studies met study selection criteria but were excluded due to the possibility that the patient populations may overlap with a later report from the same institution.

technology assessment raised concerns regarding the reference standard used in this study, citing a lack of details for how patients were histologically sampled.

The technology assessment reported on five studies (total n=196) that assessed the performance of PET in detecting distant metastasis or recurrence. Each of these studies reported information on bone metastases, while 3 reported on liver metastases, two studies reported on lung metastases, one study reported on distant lymph nodes, one study reported on a case of diffuse peritoneal metastasis, and one study discussed a case of metastasis to the pericardium. For these five studies, the technology assessment reported several study limitations, including insufficient information in all studies to determine avoidance of verification bias, lack of information in two studies to determine if a prospective design was used, and confirmed blinding of PET interpretation (for all PET scans) to the reference standard in only two studies.

Overall, the technology assessment concluded that the available data "…are insufficient to determine the diagnostic performance of PET in detecting recurrence or metastasis". The assessment also determined that the available evidence is "…insufficient to permit conclusions about the diagnostic performance of PET in detecting locoregional recurrence, which includes recurrence at the brachial plexus".

D. Evaluating Response to Treatment

For this indication, PET has been proposed for patients undergoing multicourse treatment for breast cancer to provide a more accurate or earlier determination of tumor response to treatment than is possible with conventional modalities. The technology assessment identified four prospective studies (total n=103) that examined whether PET could be used to measure response to treatment.

The four identified studies assessed a range of treatment methods (neoadjuvant chemotherapy in two studies, chemohormonotherapy in one study, and hormone therapy in 1 study) using a range of reference standards (standard response criteria in one study, histopathologic response in two studies, and clinical response in one study). All of the studies exhibited small sample sizes (n=11, 22, 30 and 40), lack of information to determine whether verification bias was avoided, and lack of information to determine whether investigators who assessed the reference standard were blinded to PET results. Only one study provided clear information to affirm that PET results were assessed blind to reference standard results. Based on these issues, the technology assessment concluded "due to limitations in its quantity, quality, and consistency the available evidence is insufficient to permit conclusions about the diagnostic performance of PET in evaluating response to treatment".

MCAC

On June 19, 2001, the MCAC Diagnostic Imaging Panel met to discuss the use of FDG-PET for the diagnosis, staging and re-staging of breast cancer. The full transcript

from the June 19th MCAC meeting is available at http://www.hcfa.gov/coverage/download/8b1-g2.txt. The panel was asked to consider a series of questions:

1. Is there adequate evidence that PET can improve health outcomes when used to decide whether to perform a biopsy in patients with an abnormal mammogram or palpable mass?

2. Is there adequate evidence that PET can improve health outcomes by leading to earlier and more accurate diagnosis of breast cancer compared to short-interval mammographic (3-6 months) follow-up in patients with low suspicion findings on mammography and other routine imaging procedures?

3. Is there adequate evidence that PET can improve health outcomes when used to determine whether to perform axillary lymph node dissection? If so, is a more detailed analysis of sentinel node biopsy vs. PET, as alternatives to axillary lymph node dissection, necessary?

4. Is there adequate evidence that PET improves health outcomes, as either an adjunct to, or a replacement for, standard staging tests in detecting locoregional recurrence or distant metastases/recurrence?

5. Is there adequate evidence that PET can improve health outcomes by providing either a more accurate or an earlier determination of tumor response to treatment compared to the use of conventional response criteria, which may rely upon clinical exam and/or standard imaging tests (e.g., CT, MRI, bone scan)?

If the answer to any question was yes, the Diagnostic Imaging Panel was asked to place the size and direction of effectiveness into one of seven categories[3].

In answering Questions 1, 2, 3, and 5, the panel unanimously agreed that there was not adequate evidence that PET can improve health outcomes for these indications. With respect to Question 4, there was extensive discussion by the panel and a decision was made to replace the original Question 4 with the following two questions:

- Is there adequate evidence that PET improves health outcomes as an adjunct to standard staging tests in detecting locoregional recurrence or distant metastases/recurrence when results from other tests are inconclusive?

- Is there adequate evidence that PET improves health outcomes as a replacement for standard imaging tests in detecting locoregional recurrence or distant metastases/recurrence?

[3] Details of the MCAC Executive Committee's Recommendations for Evaluating Effectiveness are available at http://www.hcfa.gov/coverage/8b1-I9.htm

For the first of these two questions, the Diagnostic Imaging Panel voted that there is adequate evidence that PET improves health outcomes for this indication, with five votes in the affirmative and one abstention. The panel was unable to reach consensus on the size and direction of effectiveness. For the second of these questions, the panel voted unanimously in the negative.

The discussion of the Diagnostic Imaging panelists forwarded the notion that PET scanning should have an adjunctive role to other imaging techniques during staging for breast cancer. A small study by Hathaway et al. (1999) involving patients with suspected recurrent local-regional disease was noted by the panel, in addition to anecdotal data described by a physician member of the audience (Richard Wahl) on the issue of brachial plexus recurrence. Although hampered by some key biases, such as the small sample size (n = 10) and the lack of an independent gold standard, the Hathaway study indicated some incremental value of PET over MRI in the detection of metastatic disease. Dr. Wahl reported that in his series of 15 cases from the University of Michigan, "PET consistently performed more accurately than MRI."

There was lengthier panel discussion on a diagnostic trial by Bender et al. (1997), which compared PET to CT and/or MRI in the evaluation of 75 patients for recurrent disease. There were mixed results according to recurrent tumor site, as PET often, but not uniformly, outperformed CT/MRI in terms of sensitivity. Accordingly, this article lends support to the notion that combination of different imaging modalities may provide a more optimal approach to patient care. However, the panel highlighted some drawbacks of this study: (1) only 63/75 patients received the comparative imaging techniques (CT and/or MRI) and (2) there were concerns about the specification of an independent gold standard in all 75 patients.

Dr. Sam Gambhir raised an additional item during the public comments period of the Diagnostic Imaging Panel Meeting. Dr. Gambhir discussed the potential use of PET for patient populations underserved by mammography and other routine imaging tests. While several categories of underserved women were mentioned, including women with surgically altered breast tissue or scarring from previous breast biopsy, the discussion focused primarily on women with dense breast tissue.

Dr. Gambhir presented concerns that women with dense breast tissue are not well served by mammography, with tumors often missed, even after repeated mammograms. He indicated that PET represents an alternative, more effective imaging modality for these women, since tissue density does not interfere with the PET mechanism of imaging (measurement of glucose metabolism) in the same way as techniques that rely on imaging physical structures alone. The Diagnostic Imaging Panel deliberated on this issue and raised several concerns. Some members indicated that other imaging techniques, such as ultrasound in conjunction with mammography, may provide a viable alternative for imaging dense breast tissue. Further, panelists emphasized that the questions posed to the panel did not address the issue of PET as a screening tool, and CMS referred to statutory limitations that preclude Medicare coverage for screening (with mammography as a statutorily prescribed exception). Without a more thorough review of the literature,

panelists did not feel prepared to make a recommendation on the use of PET for this population. However, the panel recommended that CMS examine this issue more thoroughly in its ongoing review of PET for breast cancer diagnosis.

In a meeting on October 17, 2001, the MCAC EC voted approval of all of the recommendations of the Diagnostic Imaging Panel except number 4. They voted to amend question number 4 to state, "is it likely that PET improves health outcomes when used as an adjunct to standard staging tests in detecting locoregional recurrence or distant metastases recurrence for some patients when results from other tests are inconclusive."

CMS Conclusions

A. Initial Diagnosis of Breast Cancer

The technology assessment and the MCAC EC determined that there was not adequate evidence to conclude that FDG PET has clinical utility in patient management (42 CFR 410.32) when used for the initial diagnosis of breast cancer. We are concerned that the pooled 89% sensitivity equates to an 11% false-negative rate and harm could result from a delay in treatment if an FDG PET scan misses malignant lesions to such an extent. Also, coverage of this indication would result in too many unnecessary biopsies with the false-positive rate of 20%. CMS has determined that the use of FDG PET is not reasonable and necessary for the initial diagnosis of breast cancer under §1862(a)(1)(A) of the Social Security Act. Therefore, Medicare will continue to have national noncoverage of this indication.

B. Initial Staging of Axillary Lymph Nodes

The technology assessment and the MCAC EC determined there was not adequate evidence to conclude that FDG PET has clinical utility in patient management (42 CFR 410.32) when used for the initial staging of axillary lymph nodes. The pooled 81% sensitivity of PET for non-palpable axillary lymph nodes provides an unacceptable degree of confidence in PET for clinicians engaged in surgical planning/staging.

Following logic similar to the clinical evaluation for primary lesion characterization, the relatively large false-negative rate (19%) allows for the frequent undertreatment of patients who have axillary disease. In other words, such patients could be denied the benefit of axillary lymph node dissection if the treating physician relied upon negative PET results. Although the pooled specificity of 95% is more encouraging, please note that any false-positive rate means that some morbidity will be incurred from dissections in patients who are truly free of axillary disease (i.e., dissection is routinely planned for anyone with presumed axillary disease via positive PET results). CMS has determined that FDG PET is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore, Medicare will continue to have national non-coverage of this indication.

C. Detection of Locoregional Recurrence or Distant Metastasis/Recurrence (Staging and Restaging)

Although the technology assessment and the MCAC EC stated that the evidence had methodological shortfalls, the MCAC EC determined that the evidence was sufficient to conclude that FDG PET has clinical utility in patient management (42 CFR 410.32) when used as an adjunct to other conventional anatomic imaging modalities in the detection of locoregional recurrence or distant metastasis.

CMS has reviewed their findings and evaluated the subject studies and has therefore determined that FDG PET is reasonable and necessary under §1862(a)(1)(A) of the Social Security Act when used as an adjunct to other conventional anatomical imaging modalities in the detection of locoregional recurrence or distant metastasis. Studies by Bender and Hathaway have provided such evidence for locoregional recurrence. Also, five other studies (also including Bender) in the technology assessment indicate that PET may confer advantages over conventional imaging in the detection of distant metastasis/recurrence, even given design shortfalls in these studies (e.g., poor delineation of reference standards). Internal CMS staff review of these studies, independent of the technology assessment, showed that FDG PET could have a positive adjunctive diagnostic role when used with standard imaging technology.

D. Evaluating Response to Treatment

The technology assessment stated that methodological problems with four small studies did not provide sufficient evidence to conclude that FDG PET was useful for evaluating response to treatment. CMS re-evaluated the studies, applied the sensitivity/specificity data from restaging studies, consulted with oncologists and PET experts, and concluded that the entire body of information was sufficient to show that FDG PET has clinical utility in the management of patients when used to evaluate response to treatment. Since breast cancer typically responds quickly to therapy, if it responds at all, women with locally advanced tumors and metastatic breast cancer may require frequent changes in chemotherapy early in the course of treatment rather than at the end of treatment. The articles by Smith and Schelling, in particular, show promising Receiver Operating Characteristic (ROC) data which demonstrate decreased tracer uptake pursuant to completion of chemotherapy. The latter study's ROC curve demonstrates the ability of PET to predict histopathological regression. Additionally, expert opinion from onocologists interviewed by CMS points to the efficacy of FDG PET for this indication. Thus, despite some potential bias among the evaluated studies, CMS has determined that sufficient evidence is present to conclude that FDG PET is reasonable and necessary under §1862(a)(1)(A) of the Social Security Act when used to monitor tumor response during therapy.

Presently, the Coverage Issues Manual, Section 50-36, prohibits coverage of monitoring tumor response during therapy when no change in therapy is being contemplated. Since we have decided to cover monitoring when a change in therapy is contemplated, we do not believe this prohibition to be applicable.

National Medicare Coverage Policy Decision

CMS will provide coverage for FDG PET full- and partial-ring scanners as an adjunct to standard imaging modalities for staging patients with distant metastasis or restaging patients with locoregional recurrence or metastasis. In addition, CMS will cover FDG PET as an adjunct to standard imaging modalities for monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer. CMS will continue to have a national noncoverage policy for the use of FDG PET for the initial diagnosis of breast cancer and the staging of axillary lymph nodes.

In regards to the dense breast issue, CMS did not address this issue since it was not a part of the request. If anyone would like to submit a specific request for the use of FDG PET for use with women who have dense breast tissue, it will be reviewed in a separate national coverage policy determination process.

(The information contained here represents only the first step towards completion of the national coverage determination (NCD). The NCD is not complete until it is formally published in the Coverage Issues Manual (CIM). Therefore, the effective date of this decision will be the effective date of the policy change published in the CIM.)